

A Pan-BCL2 inhibitor renders bone-marrow-resident human leukemia stem cells sensitive to tyrosine kinase inhibition.

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Public Summary:

Leukemia stem cells (LSCs) play a pivotal role in the resistance of chronic myeloid leukemia (CML) to tyrosine kinase inhibitors (TKIs) and its progression to blast crisis (BC), in part, through the alternative splicing of self-renewal and survival genes. To elucidate splice-isoform regulators of human BC LSC maintenance, we performed whole-transcriptome RNA sequencing, splice-isoform-specific quantitative RT-PCR (qRT-PCR), nanoproteomics, stromal coculture, and BC LSC xenotransplantation analyses. Cumulatively, these studies show that the alternative splicing of multiple prosurvival BCL2 family genes promotes malignant transformation of myeloid progenitors into BC LSCs that are quiescent in the marrow niche and that contribute to therapeutic resistance. Notably, sabutoclax, a pan-BCL2 inhibitor, renders marrow-niche-resident BC LSCs sensitive to TKIs at doses that spare normal progenitors. These findings underscore the importance of alternative BCL2 family splice-isoform expression in BC LSC maintenance and suggest that the combinatorial inhibition of prosurvival BCL2 family proteins and BCR-ABL may eliminate dormant LSCs and obviate resistance.

Scientific Abstract:

Leukemia stem cells (LSCs) play a pivotal role in the resistance of chronic myeloid leukemia (CML) to tyrosine kinase inhibitors (TKIs) and its progression to blast crisis (BC), in part, through the alternative splicing of self-renewal and survival genes. To elucidate splice-isoform regulators of human BC LSC maintenance, we performed whole-transcriptome RNA sequencing, splice-isoform-specific quantitative RT-PCR (qRT-PCR), nanoproteomics, stromal coculture, and BC LSC xenotransplantation analyses. Cumulatively, these studies show that the alternative splicing of multiple prosurvival BCL2 family genes promotes malignant transformation of myeloid progenitors into BC LSCs that are quiescent in the marrow niche and that contribute to therapeutic resistance. Notably, sabutoclax, a pan-BCL2 inhibitor, renders marrow-niche-resident BC LSCs sensitive to TKIs at doses that spare normal progenitors. These findings underscore the importance of alternative BCL2 family splice-isoform expression in BC LSC maintenance and suggest that the combinatorial inhibition of prosurvival BCL2 family proteins and BCR-ABL may eliminate dormant LSCs and obviate resistance.

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